REMARKS

FORMAL MATTERS:

Claims 5-7, 19-22, 24-29 and 31-41 are pending after entry of the amendments set forth herein.

Claim 22 is amended.

No new matter has been added.

INTERVIEW SUMMARY

Applicants wish to express their gratitude to Examiners Chernyshev and Ulm for the generosity of their time in conducting the telephonic interview with James Diehl and the undersigned on July 12, 2005.

During the interview the rejections of the claims under §112, ¶1 for lack of written description, and under §101 and §112, ¶1 for lack of utility and for lack of enablement in view of the utility rejection were discussed.

With respect to the written description rejection under §112, ¶1, the Examiner kindly noted that the recitation of the rejected claims was in error, and that only claims that included the limitation "wherein said polynucleotide molecule encodes a polypeptide that binds Grb7", and claims dependent or ultimately dependent thereon, should have been included in this rejection. These claims are claims 22, and 24-31. Furthermore, it was agreed that the written description rejection would be withdrawn if the claims were amended to remove recitation of function, namely the requirement that the encoded polypeptide bind to Grb7. Claim 22 is amended, and thus this rejection should be withdrawn.

As to the claim rejections which center on the issue of utility, Applicants explained their position that the claimed invention meets utility requirement since the claimed polynucleotides encode a protein that specifically bind to the known tumor markers GRB7 and GRB14. The Examiners suggested that Applicants bolster this assertion by providing evidence that 1) GRB7 and/or GRB14 are recognized as markers for cancer at the time of filing of the present application; and 2) the polypeptide encoded by the claimed polynucleotide specifically binds to GRB7 and/or GRB14. These issues are addressed below.

REJECTIONS UNDER §112, ¶1 – WRITTEN DESCRIPTION

Claims 5-7, 20, 22, 24-26, 31-36 and 38 were rejected on the grounds that the claimed invention is not adequately described in the specification. This rejection is traversed as applied and as it may be applied to the pending claims.

As discussed above, during the Interview, the Examiner kindly noted that the recitation of the rejected claims was in error. Only claims 22 and 24-31, which include the limitation "wherein said polynucleotide molecule encodes a polypeptide that binds Grb7", and claims dependent or ultimately dependent thereon, should have been included in this rejection.

During the Interview the Examiners kindly clarified that the written description rejection was based on the inclusion of the functional language, namely the limitation "wherein said polynucleotide molecule encodes a polypeptide that binds Grb7". It was agreed that the written description rejection would be withdrawn if the claims were amended to remove this language. Claim 22 is amended accordingly.

Withdrawal of this rejection is respectfully requested.

REJECTIONS UNDER §101 AND §112, ¶2

Claims 5-7, 19-22, 24-28 and 31-41 were rejected under §101 on the grounds that the claimed invention has no apparent or disclosed specific and substantial credible utility, and were similarly rejected under §112, ¶1 on the grounds that in view of this asserted lack of utility, the claimed invention is also not enabled. This rejection is respectfully traversed.

During the Interview, Applicants explained that the claimed invention has at least two utilities:

1) The claimed polynucleotides are useful in distinguishing cancer cells from normal cells, e.g., breast cancer cells

2) The claimed polynucleotides are useful for distinguishing cancer cells from normal cells since they encode a polypeptide that binds to Grb7 and to Grb14, each of which are known to be differentially expressed in cancer cells relative to normal cells

It is the second utility which was the focus of the discussion during the Interview, and is accordingly the focus of this response. However, Applicants specifically incorporate all prior arguments

and positions here, although they are not reiterated in their entirety in this response for purposes of clarity and brevity. All such arguments and positions continue to be maintained.

During the Interview Applicants pointed out that the second asserted utility – which exploits binding of the 2.2412 polypeptide encoded by the claimed polynucleotides to detect Grb7 or Grb14 – was not fully considered in the prior Office Action. Applicants clarified that Grb7 and Grb14 are *already known to be differentially expressed in cancer cells compared to normal cells*. Thus this second asserted utility is independent of the first asserted utility which focuses upon differential expression of the claimed 2.2412-encoding polynucleotide itself.

Instead this second asserted utility lies in the fact that the claimed polynucleotides encode 2.2412 polypeptides bind to Grb7 and Grb14 polypeptides, and thus can be used to detect Grb7 and Grb14. Detection of Grb7 and Grb14 is useful since these proteins are differentially expressed in cancerous cells relative to normal cells. That is, the claimed polynucleotides have a specific, substantial and credible utility in that the polynucleotides encode polypeptides that can be used to detect Grb7 and Grb14 and assess levels of these proteins in cells to facilitate distinguishing normal cells from cancerous cells.

The Examiners suggested during the Interview that Applicants bolster this assertion by providing evidence that 1) Grb7 and/or Grb14 are recognized as markers for cancer at the time of filing of the present application; and 2) the polypeptide encoded by the claimed polynucleotide specifically binds to Grv7 and/or Grb14. These issues are addressed below.

1) Grb7 and Grb14 Are Recognized As Markers For Cancer At The Time Of Filing Of The Present Application

Prior to the filing of the instant application, Grb7 family members, including Grb7 and Grb14, were known to be differentially expressed in human cancer cells compared to normal cells. For a review, see Daly (Daly "The Grb7 Family of Signalling Proteins" *Cell Signal* (1998) 10:613-618)[1], especially text bridging pages 614-615, Exhibit A).

In particular, at the time of filing Grb7 was known to be differentially expressed in several different cancer types. Stein et al. reported that Grb7 is overexpressed in both breast cancer cells line and in breast cancer tissues relative to normal breast tissue (see, e.g., Stein et al. "The SH2 domain

[1] Although this reference was published after the September 23, 1997 priority date, the reference is a ***review*** which cites, in relevant portion, ONLY papers published prior to the priority date.

protein GRB-7 is co-amplified, overexpressed and in a tight complex with HER2 in breast cancer." EMBO J. (Mar. 1994) 13(6):1331-40 (Exhibit B), e.g., at page 1333, col. 2). Kishi et al. reported that Grb7 is elevated in gastric tumor tissue with little or no expression in normal gastric tissue (Kishi et al. "Molecular cloning of human GRB-7 co-amplified with CAB1 and c-ERBB-2 in primary gastric cancer." Biochem Biophys Res Commun. (March 1997) 232(1):5-9 (Exhibit C), see, e.g., page 7, text bridging cols. 1 and 2). Tanaka et al reported that coexpression of Grb7 and EGFR or Her2/erbB2 was significantly related to the depth of tumor invasion in esophageal cancer (Tanaka et al. "Coexpression of Grb7 with epidermal growth factor receptor or Her2/erbB2 in human advanced esophageal carcinoma." Cancer Res. (Jan 1997) 57(1):28-31 (Exhibit D), see, e.g., page 29, col. 1 to page 30, col. 2).

Grb14 was also known to be differentially expressed prior to the filing of the instant application. Daly et al. ("Cloning and Characterization of *GRB14*, a Novel Member of the GRB7 Gene Family" *J. Biol. Chem.* (1996) 271:12502-12510, Exhibit E) reported that GRB14 expression was undetectable in normal prostate cell lines, but was detectable in prostate cancer cell lines. GRB14 expression was also undetectable in ER- breast cancer cell lines, although it was expressed in most normal human breast epithelial cell lines test. Thus Daly et al. conclude that the data demonstrated a correlation between GRB14 expression and estrogen receptor positivity in human breast cancer cells and marked overexpression in prostate cancer lines (Exhibit E, page 12509, col. 2).

2) The 2.2412 Polypeptide Encoded By The Claimed Polynucleotide Specifically Binds To Grv7 and/or Grb14

The application as filed provides evidence that the 2.2412 polypeptide, which is encoded by the claimed polynucleotides, binds to Grb7 and to Grb14 (see specification pages 10-11).

First, 2.2412 was identified by its binding to Grb14 in a yeast two-hybrid assay. cDNAs encoding the "full-length", N- or C-terminal regions of the polypeptide of the "original" 2.2412 clone were identified in a yeast two-hybrid assay as part of GST-fusion protein construct, with Grb14 used as "bait" (specification page 6, line 26 to page . This "original" 2.2412 clone encoded only a portion of SEQ ID NO:2 (from nucleotides 694-2664 of SEQ ID NO:1, which encode amino acids 232-888 SEQ ID NO:2). The N-terminal portion of this clone corresponded to nucleotides 694-1614 of SEQ ID NO:1, which encode amino acid residues 232-538 of SEQ ID NO:2. The C-terminal portion corresponded to nucleotides 1615-2664 of SEQ ID NO;1, which encode amino acid residues 539-888.

The fusion proteins were then incubated with detectably labeled Grb14 or human breast cancer cells expressing high levels of Grb7. The data showed that the fragment of the 2.2412 encoded by the "original" clone (amino acids 232-888 of SEQ ID NO:2) specifically bound Grb7 and specifically bound Grb14 (specification page 11, lines 3-6). The N-terminal portion (amino acids 232-538) bound to Grb7 and Grb14 more strongly than the C-terminal portion, indicating that the N-terminus contains a domain that mediates Grb7/Grb14 binding by the 2.2412 fragment encoded by the "original" clone.

A later publication from the laboratory of the co-inventor Roger Daly provides further evidence of specific binding of 2.2412 – later termed "tankyrase 2" – to Grb14. Lyons et al. ("Identification of a novel human tankyrase through its interaction with the adaptor protein Grb14" J Biol Chem. (May 2001) 276(20):17172-80 (Epub 2001 Feb 22) (Exhibit F)) prepared a series of deletion constructs of tankyrase 2 (2.2412) and found that Grb14 binding was primarily mediated by the N-terminal set of repeats in the tankyrase 2 (2.2412) (see Lyons et al. page 17177). In addition, Lyons et al. showed that tankyrase 2 (2.2412) and Grb14 co-immunoprecipitate, indicating that these proteins specifically bind to one another in vivo (Lyons et al., test bridging pages 17177-17178).

In view of the above, Applicants respectfully request withdrawal of the rejections of the claims under §101 for lack of utility, and under §112, ¶1 for lack of enablement.

CONCLUSION

Applicant submits that all of the claims are in condition for allowance, which action is requested. If the Examiner finds that a telephone conference would expedite the prosecution of this application, please telephone the undersigned at the number provided.

The Commissioner is hereby authorized to charge any underpayment of fees associated with this communication, including any necessary fees for extensions of time, or credit any overpayment to Deposit Account No. 50-0815, order number RICE-012.

Respectfully submitted,
BOZICEVIC, FIELD & FRANCIS LLP

Date: July 25, 2005

By: _____
Carol L. Francis
Registration No. 36,513

Enclosures:

Exhibit A:	Daly "The Grb7 Family of Signalling Proteins" *Cell Signal* (1998) 10:613-618.
Exhibit B:	Stein et al. "The SH2 domain protein GRB-7 is co-amplified, overexpressed and in a tight complex with HER2 in breast cancer." EMBO J. (Mar. 1994) 13(6):1331-40
Exhibit C:	Kishi et al. "Molecular cloning of human GRB-7 co-amplified with CAB1 and c-ERBB-2 in primary gastric cancer." Biochem Biophys Res Commun. (March 1997) 232(1):5-9
Exhibit D:	Tanaka et al. "Coexpression of Grb7 with epidermal growth factor receptor or Her2/erbB2 in human advanced esophageal carcinoma." Cancer Res. (Jan 1997) 57(1):28-31
Exhibit E:	Daly et al. "Cloning and Characterization of *GRB14*, a Novel Member of the GRB7 Gene Family" *J. Biol. Chem.* (1996) 271:12502-12510
Exhibit F:	Lyons et al. "Identification of a novel human tankyrase through its interaction with the adaptor protein Grb14" J Biol Chem. (May 2001) 276(20):17172-80 (Epub 2001 Feb 22)

BOZICEVIC, FIELD & FRANCIS LLP
1900 University Avenue, Suite 200
East Palo Alto, California 94303
Telephone: (650) 327-3400
Facsimile: (650) 327-3231